(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/74806 A1

(51) International Patent Classification[7]: C07D 401/14, 405/14, 409/14, 211/68, A61K 31/4523, A61P 25/04, 25/00

(21) International Application Number: PCT/SE01/00708

(22) International Filing Date: 30 March 2001 (30.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0001208-8 4 April 2000 (04.04.2000) SE

(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BROWN, William [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA). WALPOLE, Christopher [GA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA).

(74) Agent: ASTRAZENECA AB; Global Intellectual Property, S-151 85 Södertälje (SE).

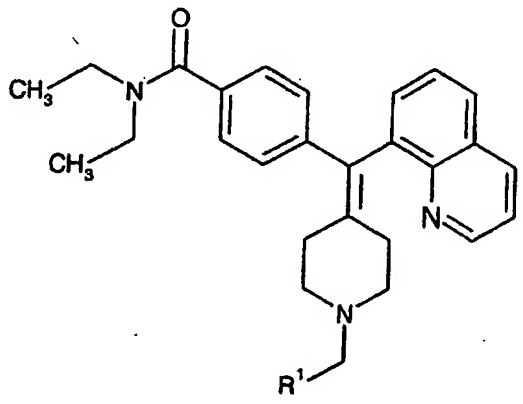
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: QUINOLINYL-PIPERIDIN-4-YLIDENE-METHYL-BENZAMIDE DERIVATIVES FOR THE TREATMENT OF PAIN



(I)

(57) Abstract: Compounds of general formula (I), where R^1 is selected from any one of phenyl, pyridinyl, thienyl, furanyl, imidazolyl, and triazolyl; where each R^1 phenyl ring and R^1 heteroaromatic ring may optionally and independently be further substituted by 1, 2 or 3 substituents selected from straight and branched C_1-C_6 alkyl, NO_2, CF_3, C_1-C_6 alkoxy, chloro, fluoro, bromo, and iodo. The substitutions on the phenyl ring and on the heteroaromatic ring may take place in any position on said ring systems; are disclosed and claimed in the present application, as well as their pharmaceutically acceptable salts and pharmaceutical compositions comprising the novel compounds and their use in therapy, in particular in the management of pain.

WO 01/74806 A1

QUINOLINYL-PIPERIDIN-4-YLIDENE-METHYL-BENZAMIDE DERIVATIVES FOR THE TREATMENT OF PAIN

Field of the invention

The present invention is directed to novel compounds, to a process for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are useful in therapy, and in particular for the treatment of pain.

Background and prior art

The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been shown to possess immunomodulatory activities.

The identification of at least three different populations of opioid receptors (μ, δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or more of these receptors has been activated.

With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. One example of a non-peptidic δ-agonist is SNC80 (*Bilsky E.J. et al., Journal of Pharmacology and Experimental Therapeutics, 273(1), pp. 359-366 (1995)*). There is however still a need for selective δ-agonists having not only improved selectivity, but also an improved side-effect profile.

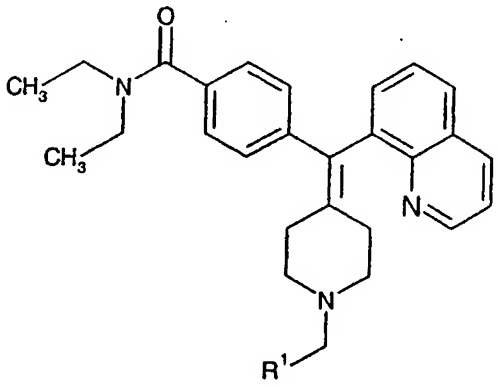
Thus, the problem underlying the present invention was to find new analgesics having improved analgesic effects, but also with an improved side-effect profile over current μ agonists, as well as having improved systemic efficacy.

Analgesics that have been identified and are existing in the prior art have many disadvantages in that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that preferred δ agonist compounds, described within the prior art, show significant convulsive effects when administered systemically.

We have now found that certain compounds not specifically disclosed by, but included within the scope of WO 98/28275, exhibit surprisingly improved δ-agonist properties and in vivo potency.

Outline of the invention

The novel compounds according to the present invention are defined by the formula I

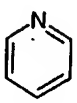


I

wherein

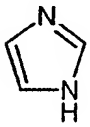
R^1 is selected from any one of

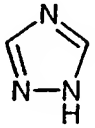
(i) phenyl;

(ii) pyridinyl  ;

(iii) thienyl  ;

(iv) furanyl  ;

(v) imidazolyl  ;

(vi) triazolyl  ;

where each R^1 phenyl ring and R^1 heteroaromatic ring may optionally and independently be further substituted by 1, 2 or 3 substituents selected from straight and branched C_1-C_6 alkyl, NO_2, CF_3, C_1-C_6 alkoxy, chloro, fluoro, bromo, and iodo. The substitutions on the phenyl ring and on the heteroaromatic ring may take place in any position on said ring systems;

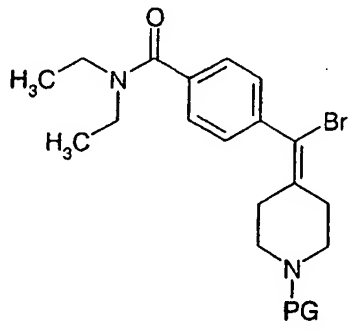
A preferred embodiment of the present invention is a compound according to figure I wherein R^1 is as defined above and each R^1 phenyl ring and R^1 heteroaromatic ring may independently be further substituted by a methyl group.

A more preferred embodiment of the present invention is a compound according to figure I wherein R^1 is pyridinyl, thienyl or furanyl.

Within the scope of the invention are also salts and enantiomers of the compounds of the formula I, including enantiomers of salts.

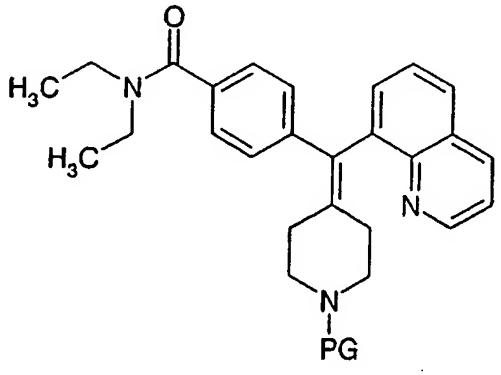
When the phenyl ring and the heteroaromatic ring(s) are substituted, the preferred substituents are selected from anyone of CF_3, methyl, iodo, bromo, fluoro and chloro.

Reaction step g in Scheme 1, *vide infra*, is performed by reacting an intermediate compound of the general formula II



II

wherein PG is a urethane or benzyl-like protecting group, such as Boc, with 8-quinolinyl boronic acid, using a palladium catalyst, e.g. $Pd(PPh_3)_4$, in the presence of a base, e.g. Na_2CO_3, to give the compounds of general formula III,



III

which is thereafter deprotected, under standard conditions and alkylated under reductive conditions with a compound of the general formula R^1-CHO to give compounds of the general formula I.

Suitable palladium catalysts include, but is not limited to, $PdCl_2$ (with a phosphine), $Pd(OAc)_2$ (with a phosphine), $Pd(dba)_2$, $PdCl_2(dppf)$ CH_2Cl_2, $Pd(PPh_3)_4$, and Pd/C.

Suitable bases include, but is not limited to, triethylamine, sodium and potassium carbonate.

Suitable reducing agents to be used includes, but is not limited to, sodium cyanoborohydride and sodium triacetoxyborohydride.

The novel compounds of the present invention are useful in therapy, especially for the treatment of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

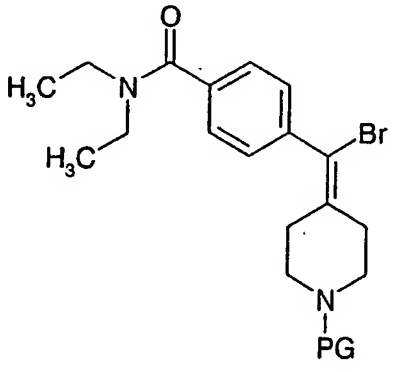
Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety, urinary incontinence, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such treatment.

A further aspect of the present invention is intermediates of the general formula II,



II

wherein PG is a urethane or benzyl-like protecting group, such as Boc,

Methods of preparation

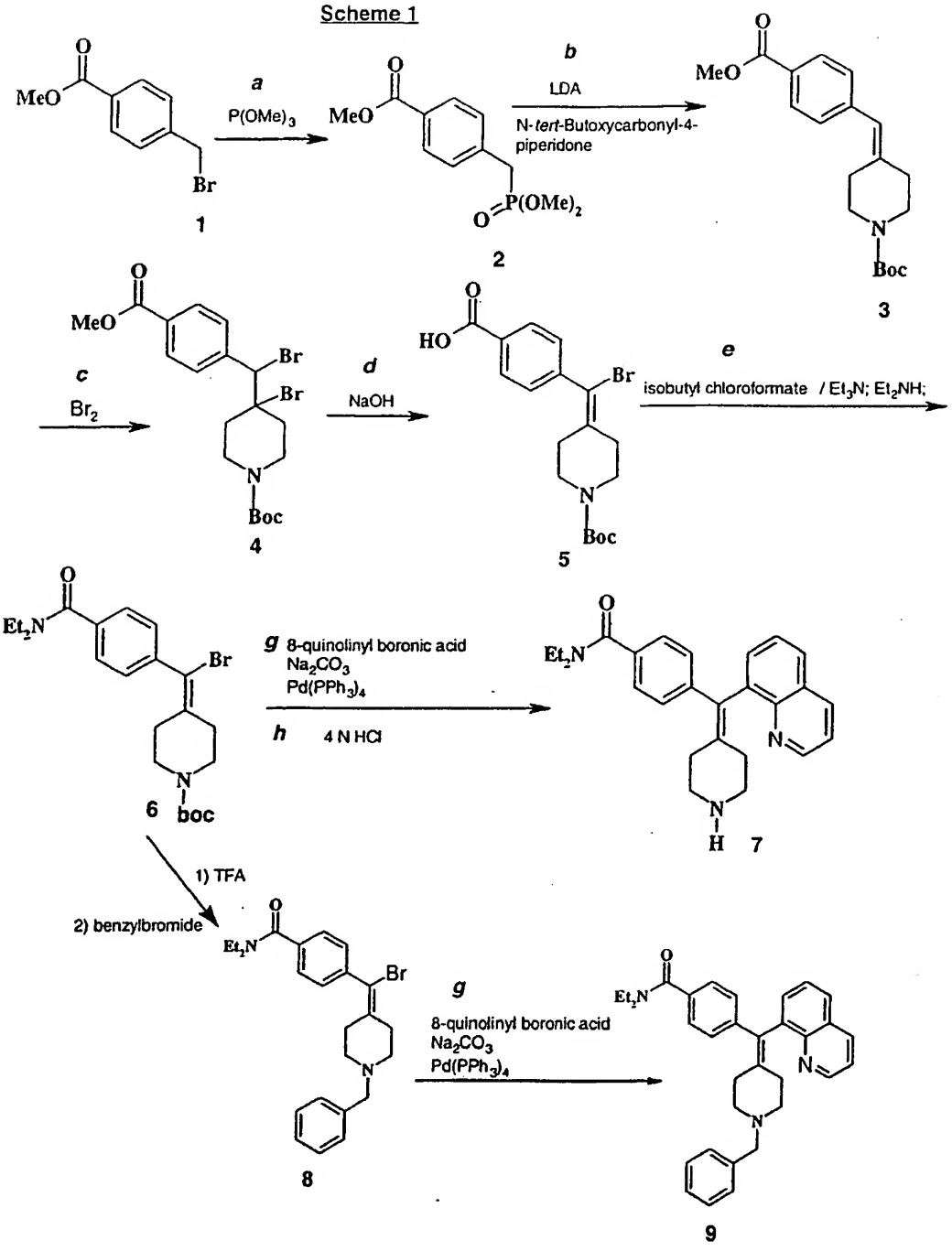
The compounds according to the present invention may be prepared by following the known procedures described in e.g. *"Advanced Organic Chemistry" third edition. by Jerry March, John Wiley and Sons Inc.; New York (1985): Step (a): p848; Step (b): p848;*

Step (c): p657; Step (d): p875; Step (e): p371-373; Step (f): p364-366; Step (g): N. Miyaura and A. Suzuki, Chem. Rev., 95, 2457-2483(1995); Step (h): "Protective Groups in Organic synthesis" p 327-329, by Theodora W. Greene and Peter G.M. Wuts, Second Edition, John Wiley and Sons Inc.; New York (1991). These references are hereby incorporated in full.

EXAMPLES

The invention will now be described in more detail by the following Examples, which are not to be construed as limiting the invention.

Scheme 1


MeO
Br
1
a
P(OMe)3
MeO
O=P(OMe)2
2
b
LDA
N-tert-Butoxycarbonyl-4-piperidone
MeO
N
Boc
3
c
Br2
Br
Br
N
Boc
4
d
NaOH
HO
Br
N
Boc
5
e
isobutyl chloroformate / Et3N; Et2NH;
Et2N
Br
N
6 boc
g 8-quinolinyl boronic acid
Na2CO3
Pd(PPh3)4
h 4 N HCl
Et2N
N
N
H 7
1) TFA
2) benzylbromide
Et2N
Br
N
8
g
8-quinolinyl boronic acid
Na2CO3
Pd(PPh3)4
Et2N
N
N
9

Example 1
Preparation of N,N-diethyl-4-(8-quinolinyl-piperidin-4-ylidene-methyl)-benzamide (compound 7)

(i) Preparation of 4-(4-methoxycarbonyl-benzylidene)-piperidine-1-carboxylic acid *tert*-butyl ester (compound 3)

A mixture of **compound 1** (11.2 g, 49 mmol) and trimethyl phosphite (25 mL) was refluxed under N_2 for 5 hrs. Excess trimethyl phosphite was removed by co-distillation with toluene to give **compound 2** in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 3.20 (d, 2H, J=22 Hz), 3.68 (d, 3H 10.8 Hz), 3.78 (d, 3H, 11.2 Hz), 3.91 (s, 3H), 7.38 (m, 2H), 8.00 (d, 2H, J=8 Hz).

(ii) To a solution of the above product (**compound 2**) in dry THF (200 mL) was added dropwise lithium diisopropylamide (32.7 mL 1.5 M in hexanes, 49 mmol) at -78 °C. The reaction mixture was then allowed to warm to room temperature prior to addition of N-*tert*-butoxycarbonyl-4-piperidone (9.76 g, 49 mmol in 100 mL dry THF). After 12 hrs, the reaction mixture was quenched with water (300 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to give a crude product, which was purified by flash chromatography to provide **compound 3** as a white solid (5.64 g, 35%):

IR (NaCl) 3424, 2974, 2855, 1718, 1 688, 1606, 1427, 1362, 1276 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.44 (s, 1H), 2.31 (t, J=5.5 Hz, 2H), 2.42 (t, J=5.5 Hz, 2H), 3.37 (t, J=5.5 Hz, 2H), 3.48 (t, J=5.5 Hz, 2H), 3.87(s, 3H), 6.33 (s, 1H), 7.20 (d J=6.7 Hz, 2H), 7.94 (d, J,=6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 29.2, 36.19, 51.9, 123.7, 127.8, 128.7, 129.4, 140.5, 142.1, 154.6, 166.8.

(iii) Preparation of 4-bromo-4-[bromo-(4-methoxycarbonyl-phenyl)-methyl]-piperidine-1-carboxylic acid tert-butyl ester (compound 4)

To a mixture of **compound 3** (5.2 g, 16 mmol) and K_2CO_3 (1.0 g) in dry dichloromethane (200 mL) was added a solution of bromine (2.9 g, 18 mmol) in 30 mL CH_2Cl_2 at 0 °C. after 1.5 hrs at room temperature, the solution after filtration of K_2CO_3 was condensed. The residue was then dissolved in ethyl acetate (200 mL), washed with water (200 mL), 0.5 M HCl (200 mL) and brine (200 mL), and dried over $MgSO_4$. Removal of solvents provided a crude product, which was recrystallized from methanol to give **compound 4** as a white solid (6.07 g, 78%): IR (NaCl) 3425, 2969, 1725, 1669, 1426, 1365, 1279, 1243 cm^{-1};

^1H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.75 (m, 2H), 1.90 (m, 2H), 2.1 (m, 4H), 3.08 (br, 4H), 3.90 (s, 3H), 4.08 (br, 4H), 5.14 (s, 1H), 7.57 (d, J=8.4 Hz, 2H) 7.98 (d, J=8.4 Hz, 2H);

^{13}C NMR ($CDCl_3$) δ 28.3, 36.6, 38.3, 40.3, 52.1, 63.2, 72.9, 129.0, 130.3, 130.4, 141.9, 154.4, 166.3.

(iv) Preparation of 4-[bromo-(4-caboxy-phenyl)-methylene]-piperidine-1-carboxylic acid tert-butyl ester (compound 5)

A solution of **compound 4** (5.4 g 11 mmol) in methanol (300 mL) and 2.0 M NaOH (100 mL) was heated at 40 °C for 3 hrs. The solid was collected by filtration, and dried overnight under vacuum. The dry salt was dissolved in 40% acetonitrile/water, and was adjusted to pH 2 using concentrated HCl. The desired product **compound 5** (3.8 g, 87%) was isolated as a white powder by filtration: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.22 (dd, J=5.5 Hz, 6.1 Hz, 2H), 2.64 (dd, J=5.5 Hz, 6.1 Hz, 2H), 3.34 (dd, J=5.5 Hz, 6.1 Hz, 2H), 3.54 (dd, J=5.5 Hz, 6.1 Hz, 2H), 7.35 (d, J=6.7 Hz, 2H), 8.08 (d, J=6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 31.5, 34.2, 44.0, 115.3, 128.7, 129.4, 130.2, 137.7, 145.2, 154.6, 170.3.

(v) Preparation of 4-[bromo-(4-diethylcarbamoyl-phenyl)-methylene]-piperidine-1-carboxylic acid tert-butyl ester (compound 6)

To a solution of **compound 5** (1.0 g, 2.5 mmol) in dry dichloromethane (10 mL) at - 20 °C was added isobutylchloroformate (450 mg, 3.3 mmol). After 20 min at -20 °C diethylamine (4 mL) was added and the reaction was allowed to warm to room temperature. After 1.5 hrs the solvents were evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over $MgSO_4$. Removal of solvents provided a crude product, which was purified by flash chromatography to give **compound 6** as white needles (800 mg, 73%): IR (NaCl) 3051, 2975, 1694, 1633, 1416, 1281, 1168, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (br, 3H), 1.22 (br, 3H), 1.44 (s, 9H), 2.22 (t, J=5.5 Hz, 2H), 2.62 (t, J=5.5 Hz, 2H), 3.33 (m, 4H), 3.55 (m, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.36 (d, J=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.71, 14.13, 28.3, 31.5, 34.2, 39.1, 43.2, 79.7, 115.9, 126.3, 129.3, 136.8, 137.1, 140.6, 154.6, 170.

(vi) <u>Preparation of N,N-diethyl-4-(8-quinolinyl-piperidin-4-ylidene-methyl)-benzamide (compound 7).</u>

A mixture of **compound 6** (902 mg, 2.0 mmol), 8-quinolinyl boronic acid (860 mg, 5.0 mmol), 2M Na_2CO_3 (2.5 mL), and tetrakis(triphenyl phosphine) palladium(0) (20 mg) in toluene (degassed, 5 mL) and ethanol (degassed, 5 mL) was refluxed at 90 °C for 4 hrs under N_2. The reaction mixture was then cooled down to r.t., and extracted with ethyl acetate (2 x 100 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to give a crude product.

The above product was treated with 4.0 M HCl in dioxane at 50 °C for 2 h. After evaporation, the residue was dissolved in 1 M HCl (100 mL) and impurities were extracted with diethyl ether (3 x 100 mL). The aqueous phase was basified with NH_4OH and extracted with dichloromethane (3 x 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated to give the **title compound 7** (729 mg, 91 %).

^1H-NMR (400 MHz, $CDCl_3$) δ 1.07 (3 H, br m, $C\underline{H}_3CH_2$-), 1.20 (3 H, br m, $CH_3C\underline{H}_2$-), 2.00 (2 H, m, piperidine C<u>H</u>-), 2.46 (1H, s, N<u>H</u>), 2.52 (2 H, m, piperidine C<u>H</u>-), 2.75 (1H, m, piperidine C<u>H</u>-), 2.92 (2 H, m, piperidine C<u>H</u>-), 3.05 (1 H, m, piperidine C<u>H</u>-), 3.22 (2

H, m, $C\underline{H}_2N$-), 3.49 (2 H, m, $C\underline{H}_2N$-), 7.23 (2 H, m, Ar<u>H</u>), 7.32 (2 H, m, Ar<u>H</u>), 7.36 (1 H, m, Ar<u>H</u>), 7.49 (2 H, m, Ar<u>H</u>), 7.72 (1 H, dd, J = 6.4, 3.2 Hz, Ar<u>H</u>), 8.11 (1 H, dd, J = 8.4, 1.6 Hz, Ar<u>H</u>), 8.91 (1 H, dd, J = 4.0, 1.6 Hz, Ar<u>H</u>); Its HCl salt: m.p. > 170 ^{0}C (Dec.); IR (NaCl) 3410, 2973, 1614, 1551, 1436, 1284 cm^{-1}.

<u>Example 2</u>

<u>Preparation of N,N-diethyl-4-(8-quinolinyl-N-benzyl-piperidin-4-ylidene-methyl)-benzamide (compound 9)</u>

(i) <u>Preparation of N,N-diethyl-4-(bromo-N-benzyl-piperidin-4-ylidene-methyl)-benzamide (compound 8)</u>

Compound **6** prepared in **Example 1(v)** above (2.26 g, 5.0 mmoL), was treated with TFA (25 mL) in dichloromethane (25 mL) at room temperature. After 2 h, the reaction mixture was condensed to give a residue, which was dissolved in acetonitrile (20 mL), and was reacted with benzyl bromide (5.0 mmol) at r.t. for 2 h. The reaction mixture was condensed, and then dissolved in ethyl acetate (100 mL). The organic solution were washed with 1N NH_4OH and brine, dried over $MgSO_4$. Removal of solvents provided a crude product, which was purified by flash chromatography to give **compound 8** as an oil (1.0 g, 45%): IR (NaCl) 2971, 1630, 1427, 1287, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (br, 3H), 1.23 (br, 3H), 2.28 (m, 2H), 2.37 (m, 2H), 2.55 (m, 2H), 2.69 (m, 2H), 3.27 (m, 2H), 3.53 (br, 4H), 7.31 (m, 4H).

(ii) <u>Preparation of N,N-diethyl-4-(8-quinolinyl-N-benzyl-piperidin-4-ylidene-methyl)-benzamide (compound 9)</u>

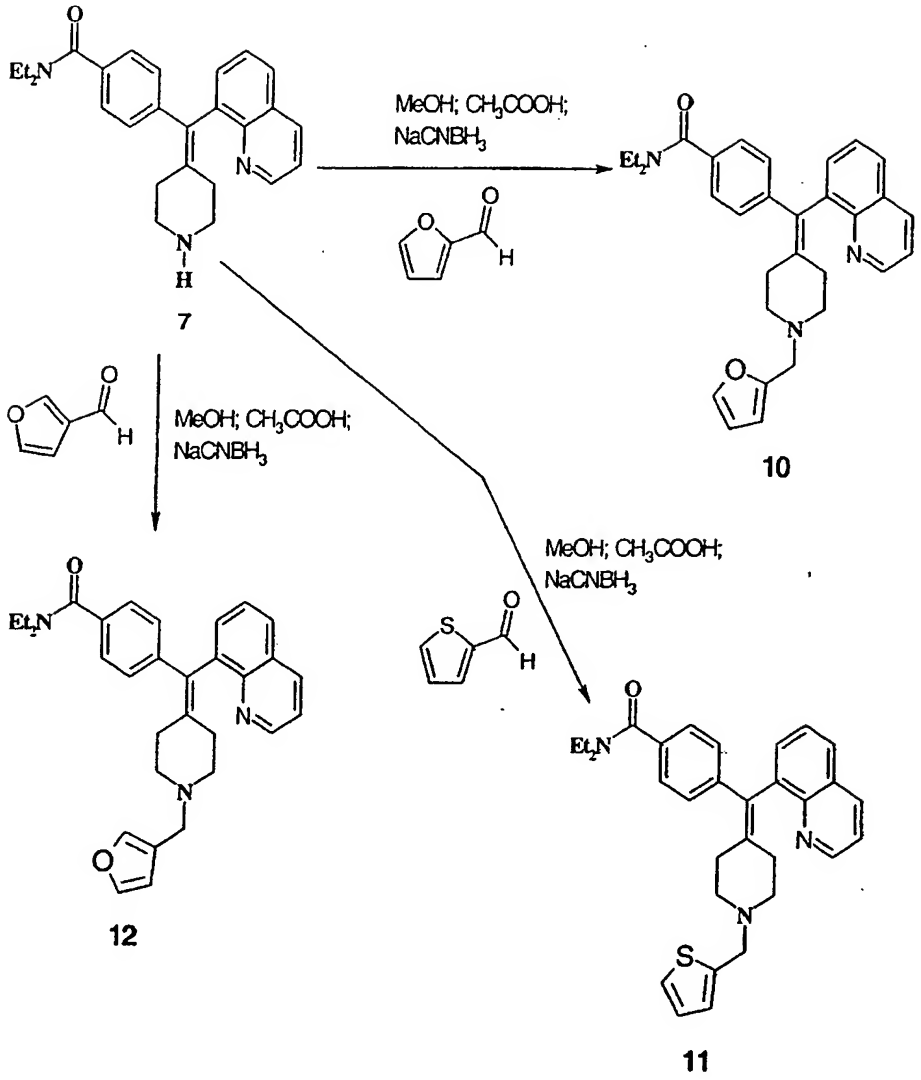
A mixture of **compound 8** prepared in step (i) above (1.32 mg, 3.0 mmol), 8-quinolinylboronic acid (1.04 mg, 6.0 mmol), 2M Na_2CO_3 (3.0 mL), and tetrakis(triphenyl phosphine) palladium(0) (20 mg) in toluene (degassed, 5 mL) and ethanol (degassed, 5 mL) was refluxed at 90 °C for 2 hrs under N_2. The reaction mixture was then cooled down to r.t., and extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$. Removal of solvents provided a crude product, which was purified by flash chromatography to give the desired **title compound 9** (832 mg,

57 %): IR (NaCl) 2971, 1625, 1551, 1426, 1287 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04 (3 H, br m, $C\underline{H}_3CH_2$-), 1.17 (3 H, br m, $C\underline{H}_3CH_2$-), 2.03 (2 H, m, piperidine C$\underline{H}$-), 2.30 (1H, m, piperidine C$\underline{H}$), 2.51 (2H, m, piperidine C$\underline{H}$), 2.59 (2 H, m, piperidine C$\underline{H}$-), 2.68 (1H, m, piperidine C$\underline{H}$-), 3.19 (2 H, m, $C\underline{H}_2N$-), 3.49 (2 H, m, $C\underline{H}_2N$-), 3.52 (2H, s, $PhC\underline{H}_2N$), 7.35(10 H, m, Ar$\underline{H}$), 7.46 (2 H, m, Ar$\underline{H}$), 7.71 (1 H, m, Ar$\underline{H}$), 8.10 (1 H, m, Ar$\underline{H}$), 8.90 (1 H, m, Ar$\underline{H}$).

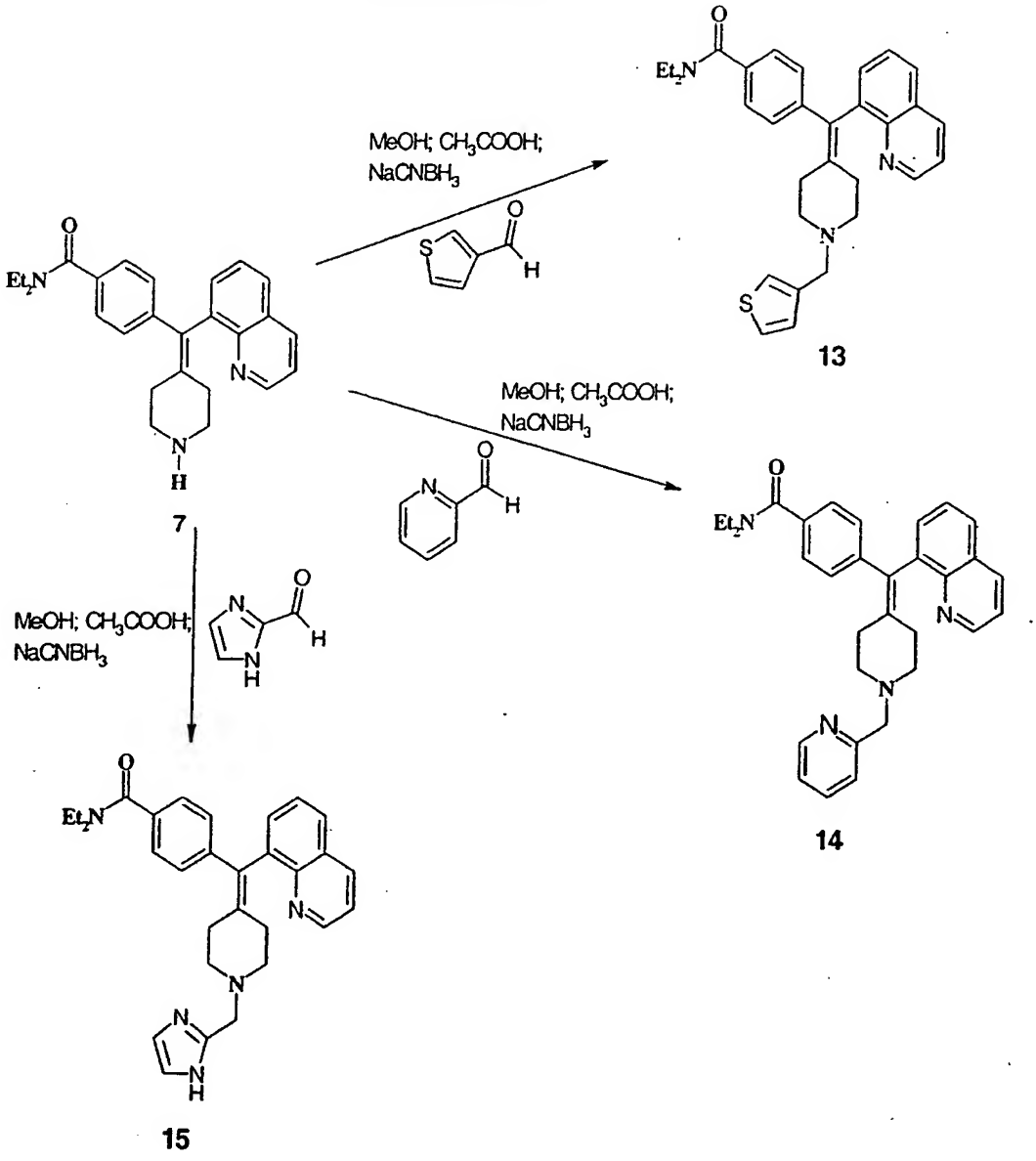
Examples 3-10

Compounds 10-17 of Examples 3-10, were prepared by following the synthetic procedures of Scheme 2 below.

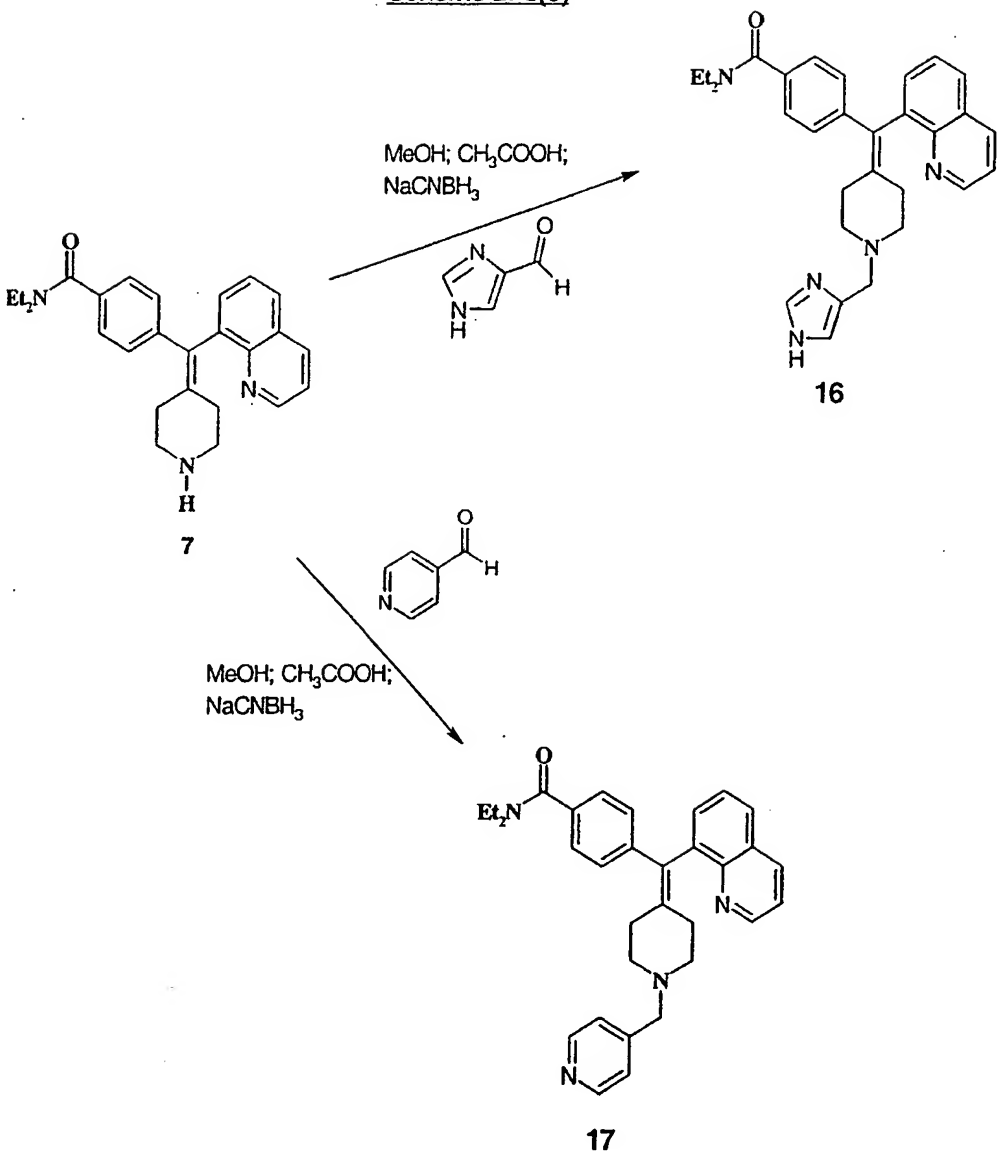
Scheme 2: 1(3)


MeOH; CH3COOH;
NaCNBH3
7
10
MeOH; CH3COOH;
NaCNBH3
MeOH; CH3COOH;
NaCNBH3
12
11

Scheme 2: 2(3)


MeOH; CH3COOH;
NaCNBH3
MeOH; CH3COOH;
NaCNBH3
MeOH; CH3COOH;
NaCNBH3
7
13
14
15

Scheme 2: 3(3)



7

16

17

Example 3

Preparation of *N,N*-diethyl-4-[[1-(2-furylmethyl)-4-piperidinylidene](8-quinoline)methyl]benzamide (compound 10)

To a room temperature solution of secondary amine (300mg; 0.75mmol) in methanol (8ml) was added 2-furaldehyde (261µl; 3.15mmol), followed by acetic acid (0.5ml). The mixture was stirred for two hours then sodium cyanoborohydride (198mg; 3.15mmol) was added. The reaction mixture was stirred overnight, then sodium hydroxide 2N was added and the mixture extracted with methylene chloride. Combined methylene chloride extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Reverse phase purification.

(M+1) calculated: 480.62, (M+1) observed: 480.16

Anal.: calculated for ($C_{31}H_{33}N_3O_2$ X 2.20 $C_2HO_2F_3$ X 1.00 H_2O): C:56.81%; H: 5.01%; N:5.61%; found: C:56.84%; H:4.96%; N:5.59%

^{1}HNMR (CD_3OD): 8.86-8.90 (m, 1H), 8.38-8.50 (m, 1H), 7.86-7.96 (m, 1H), 7.48-7.66 (M, 4H), 7.31 (d, 2H, J=7.6Hz), 7.21 (d, 2H, J=7.6Hz), 6.61-6.62 (m, 1H), 6.43-6.44 (m, 1H), 4.34 (s, 2H), 2.04-3.62 (m, 12H), 1.07-1.16 (m, 3H), 0.94-1.03 (m, 3H)

Example 4

Preparation of *N,N*-diethyl-4-{8-quinolinyl[1-(2-thienylmethyl)-4-piperidinylidene]methyl}benzamide (compound 11)

To a room temperature solution of secondary amine (300mg; 0.75mmol) in methanol (8ml) was added thiophene-2-carboxaldehyde (294.4µl; 3.15mmol), followed by acetic acid (0.5ml). The mixture was stirred for two hours then sodium cyanoborohydride (198mg; 3.15mmol) was added. The reaction mixture was stirred overnight, then sodium hydroxide 2N was added and the mixture extracted with methylene chloride. Combined methylene

chloride extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Reverse phase purification.

(M+1) calculated: 496.69, (M+1) observed: 496.09

Anal.: calculated for ($C_{31}H_{33}N_3OS$ X 2.50 $C_2HO_2F_3$ X 0.60 H_2O): C:54.63%; H:4.67%; N:5.31%; found: C:54.62%; H:4.64%; N:5.45%

^{1}HNMR (CD_3OD): 8.89-8.90 (m, 1H), 8.42-8.56 (m, 1H), 7.86-7.98 (m, 1H), 7.53 (d, 1H, J=5.2Hz), 7.50-7.70 (m, 3H), 7.30 (d, 2H, J=7.6Hz), 7.20-7.24 (m, 1H), 7.20 (d, 2H, J=8.0Hz), 7.02-7.06 (m, 1H), 4.50 (s, 2H), 2.04-3.66 (m, 12H), 1.06-1.16 (m, 3H), 0.94-1.02 (m, 3H)

Example 5

Preparation of *N,N*-diethyl-4-[[1-(3-furylmethyl)-4-piperidinylidene](8-quinolinyl)methyl]benzamide (compound 12)

To a room temperature solution of secondary amine (300mg; 0.75mmol) in methanol (8ml) was added 3-furaldehyde (272.4µl; 3.15mmol), followed by acetic acid (0.5ml). The mixture was stirred for two hours then sodium cyanoborohydride (198mg; 3.15mmol) was added. The reaction mixture was stirred overnight, then sodium hydroxide 2N was added and the mixture extracted with methylene chloride. Combined methylene chloride extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Reverse phase purification.

(M+1) calculated: 480.62, (M+1) observed: 480.33

Anal.: calculated for ($C_{31}H_{33}N_3O_2$ X 1.80 $C_2HO_2F_3$ X 0.80 H_2O): C:59.43%; H:5.25%; N:6.01%; found: C:59.38%; H:5.24%; N:5.98%

^{1}HNMR (CD_3OD): 8.80-8.88 (m, 1H), 8.30-8.42 (m, 1H), 7.80-7.92 (m, 1H), 7.44-7.68 (m, 4H), 7.26-7.36 (m, 2H), 7.16-7.24 (m, 3H), 6.50 (s, 1H), 4.15 (s, 2H), 2.86-3.62 (m, 9H), 2.48-2.66 (m, 1H), 2.06-2.36 (m, 2H), 1.06-1.16 (m, 3H), 0.94-1.04 (m, 3H)

Example 6

Preparation of *N,N*-diethyl-4-{8-quinolinyl[1-(3-thienylmethyl)-4-piperidinylidene]methyl}benzamide (compound 13)

To a room temperature solution of secondary amine (300mg; 0.75mmol) in methanol (8ml) was added thiophene-3-carboxaldehyde (276µl; 3.15mmol), followed by acetic acid (0.5ml). The mixture was stirred for two hours then sodium cyanoborohydride (198mg; 3.15mmol) was added. The reaction mixture was stirred overnight, then sodium hydroxide 2N was added and the mixture extracted with methylene chloride. Combined methylene chloride extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Reverse phase purification.

(M+1) calculated: 496.69, (M+1) observed: 496.11

Anal.: calculated for ($C_{31}H_{33}N_3OS$ X 2.70 $C_2HO_2F_3$ X 0.70 H_2O): C:53.57%; H:4.58%; N:5.15%; found: C:53.56%; H:4.54%; N:5.40%

^{1}HNMR (CD_3OD): 8.82-8.90 (m, 1H), 8.34-8.50 (m, 1H), 7.82-7.96 (m, 1H), 7.42-7.70 (m, 4H), 7.24-7.36 (m, 2H), 7.20 (d, 2H, J=7.2Hz), 7.08-7.14 (m, 2H), 4.28 (s, 2H), 2.04-3.58 (m, 12H), 1.06-1.16 (m, 3H), 0.92-1.03 (m, 3H)

Example 7

Preparation of *N,N*-diethyl-4-[[1-(2-pyridinylmethyl)-4-piperidinylidene](8-quinolinyl)methyl]benzamide (compound 14)

To a room temperature solution of secondary amine (300mg; 0.75mmol) in methanol (8ml) was added 2-pyridinecarboxaldehyde (299.6µl; 3.15mmol), followed by acetic acid (0.5ml). The mixture was stirred for two hours then sodium cyanoborohydride (198mg; 3.15mmol) was added. The reaction mixture was stirred overnight, then sodium hydroxide 2N was added and the mixture extracted with methylene chloride. Combined methylene chloride extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Reverse phase purification.

(M+1) calculated: 491.65, (M+1) observed: 491.11

Anal.: calculated for ($C_{32}H_{34}N_4O$ X 2.40 $C_2HO_2F_3$ X 1.00 H_2O): C:56.50%; H:4.95%; N:7.16%; found: C:56.47%; H:4.97%; N:7.27%

^{1}HNMR (CD_3OD): 8.91 (dd, 1H, J=4.4, 1.2Hz), 8.57 (d, 1H, J=4.4Hz), 8.47 (dd, 1H, J=8.0, 1.6Hz), 7.91 (dd, 1H, J=7.2, 2.8Hz), 7.79 (dt, 1H, J=8.0, 1.6Hz), 7.56-7.62 (m, 3H), 7.39 (d, 1H, J=7.2Hz), 7.32 (d, 2H, J=8.0Hz), 7.30-7.36 (m, 1H), 7.21 (d, 2H, J=8.4Hz), 4.41 (s, 2H), 3.08-3.56 (m, 8H), 2.72-2.88 (m, 2H), 2.18-2.36 (m, 2H), 1.06-1.16 (m, 3H), 0.92-1.02 (m, 3H)

Example 8

Preparation of *N,N*-diethyl-4-[[1-(1*H*-imidazol-2-ylmethyl)-4-piperidinylidene](8-quinolinyl)methyl]benzamide (compound 15)

To a room temperature solution of secondary amine (300mg; 0.75mmol) in methanol (8ml) was added 2-imidazolecarboxaldehyde (302.7mg; 3.15mmol), followed by acetic acid (0.5ml). The mixture was stirred for two hours then sodium cyanoborohydride (198mg; 3.15mmol) was added. The reaction mixture was stirred overnight, then sodium hydroxide 2N was added and the mixture extracted with methylene chloride. Combined methylene chloride extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Reverse phase purification.

(M+1) calculated: 480.63, (M+1) observed: 479.97

Anal.: calculated for ($C_{30}H_{33}N_5O$ X 2.80 $C_2HO_2F_3$ X 2.20 H_2O): C:50.99%; H:4.83%; N:8.35%; found: C:51.07%; H:4.90%; N:8.10%

^{1}HNMR (CD_3OD): 8.91 (dd, 1H, J=4.4, 1.2Hz), 8.60 (d, 1H, J=7.6Hz), 7.96 (dd, 1H, J=6.4, 3.6Hz), 7.62-7.68 (m, 3H), 7.39 (s, 2H), 7.30 (d, 2H, J=8.0Hz), 7.19 (d, 2H, J=8.8Hz), 4.09 (s, 2H), 3.34-3.46 (m, 2H), 3.02-3.22 (m, 4H), 2.78-2.88 (m, 2H), 2.60-2.70 (m, 2H), 2.04-2.18 (m, 2H), 1.06-1.16 (m, 3H), 0.92-1.02 (m, 3H)

Example 9

Preparation of *N,N*-diethyl-4-[[1-(1*H*-imidazol-4-ylmethyl)-4-piperidinylidene](8-quinolinyl)methyl]benzamide (compound 16)

To a room temperature solution of secondary amine (300mg; 0.75mmol) in methanol (8ml) was added 4(5)-imidazolecarboxaldehyde (302.7mg; 3.15mmol), followed by acetic acid (0.5ml). The mixture was stirred for two hours then sodium cyanoborohydride (198mg; 3.15mmol) was added. The reaction mixture was stirred overnight, then sodium hydroxide

2N was added and the mixture extracted with methylene chloride. Combined methylene chloride extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Reverse phase purification.

(M+1) calculated: 480.63, (M+1) observed: 480.15

Anal.: calculated for ($C_{30}H_{33}N_5O$ X 3.70 $C_2HO_2F_3$ X 1.20 H_2O): C:48.66%; H:4.27%; N:7.59%; found: C:48.68%; H:4.33%; N:7.49%

^{1}HNMR (CD_3OD): 8.90 (dd, 1H, J=4.4, 1.2Hz), 8.71-8.74 (m, 1H), 8.53 (d, 1H, J=8.0Hz), 7.93 (dd, 1H, J=6.4, 3.6Hz), 7.58-7.63 (m, 4H), 7.29 (d, 2H, J=8.0Hz), 7.19 (d, 2H, J=8.8Hz), 4.40 (s, 2H), 3.28-3.50 (m, 4H), 3.08-3.24 (m, 4H), 2.68-2.84 (m, 2H), 2.14-2.50 (m, 2H), 1.05-1.14 (m, 3H), 0.92-1.02 (m, 3H)

Example 10

Preparation of *N,N*-diethyl-4-[[1-(4-pyridinylmethyl)-4-piperidinylidene](8-quinolinyl)methyl]benzamide (compound 17)

To a room temperature solution of secondary amine (300mg; 0.75mmol) in methanol (8ml) was added 4-pyridinecarboxaldehyde (241mg; 2.25mmol), followed by acetic acid (0.5ml). The mixture was stirred for 30 minutes then sodium cyanoborohydride (142mg; 2.25mmol) was added. The reaction mixture was stirred overnight, then sodium hydroxide 2N was added and the mixture extracted with methylene chloride. Combined methylene chloride extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Reverse phase purification.

(M+1) calculated: 491.28, (M+1) observed: 491.09

Anal.: calculated for ($C_{32}H_{34}N_4O$ X 2.60 $C_2HO_2F_3$ X 1.50 H_2O): C:54.88%; H:4.90%; N:6.88%; found: C:54.87%; H:4.90%; N:6.75%.

^{1}HNMR (CD_3OD): 8.86-896 (m, 1H), 8.62-8.70 (m, 1H), 8.42-8.52 (m, 1H), 7.88-7.98 (m, 1H), 7.50-7.70 (m, 4H), 7.28-7.38 (m, 3H), 7.16-7.26 (m, 3H), 4.36 (s, 2H), 2.90-3.60 (m, 8H), 2.50-2.90 (m, 2H), 2.00-2.40 (m, 2H), 0.82-1.16 (m, 6H)

Pharmaceutical compositions

The novel compounds according to the present invention may be administered orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

A preferred route of administration is orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Salts include, but are not limited to pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts within the scope of the present invention include: acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucaptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate. Examples of pharmaceutically unacceptable salts within the scope of the present invention include: hydroiodide, perchlorate, and tetrafluoroborate. Preferred pharmaceutically acceptable salts are the hydrochlorides, sulfates and bitartrates. The hydrochloride and sulfate salts are particularly preferred.

The term composition is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid from compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical compositions is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

BIOLOGICAL EVALUATION

In vitro model

Cell culture

A. Human 293S cells expressing cloned human μ, δ, and κ receptors and neomycin resistance were grown in suspension at 37°C and 5% CO_2 in shaker flasks containing calcium-free DMEM10% FBS, 5% BCS, 0.1% Pluronic F-68, and 600 μg/ml geneticin.

B. Mouse and rat brains were weighed and rinsed in ice-cold PBS (containing 2.5mM EDTA, pH 7.4). The brains were homogenized with a polytron for 15 sec (mouse) or 30 sec (rat) in ice-cold lysis buffer (50mM Tris, pH 7.0, 2.5mM EDTA, with phenylmethylsulfonyl fluoride added just prior use to 0.5MmM from a 0.5M stock in DMSO:ethanol).

Membrane preparation

Cells were pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 15 min, then homogenized with a polytron for 30 sec. The suspension was spun at 1000g (max) for 10 min at 4°C. The supernatant was saved on ice and the pellets resuspended and spun as before. The supernatants from both spins were combined and spun at 46,000 g(max) for 30 min. The pellets were resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final pellets were resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes were frozen in dry ice/ethanol and stored at -70°C until use. The protein concentrations were determined by a modified Lowry assay with sodium dodecyl sulfate.

Binding assays

Membranes were thawed at 37°C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM $MgCl_2$, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which was stored at 4°C after filtration through a 0.22 m filter, and to which had been freshly added 5 μg/ml aprotinin, 10 μM bestatin, 10 μM diprotin A, no DTT). Aliquots of 100 μl were added to iced 12x75 mm polypropylene tubes containing 100 μl of the appropriate radioligand and 100 μl of test compound at various concentrations. Total (TB) and nonspecific (NS) binding were determined in the absence and presence of 10 μM naloxone respectively. The tubes were vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM $MgCl_2$) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethyleneimine. The radioactivity (dpm) retained on the filters was measured with a beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep well plates, the filtration is over 96-place PEI-soaked unifilters, which were washed with 3 x 1 ml wash buffer, and dried in an oven at 55°C for 2h. The filter plates were counted in a TopCount (Packard) after adding 50 μl MS-20 scintillation fluid/well.

Functional Assays

The agonist activity of the compounds is measured by determining the degree to which the compounds receptor complex activates the binding of GTP to G-proteins to which the receptors are coupled. In the GTP binding assay, GTP[γ]^{35}S is combined with test compounds and membranes from HEK-293S cells expressing the cloned human opioid receptors or from homogenised rat and mouse brain. Agonists stimulate GTP[γ]^{35}S binding in these membranes. The EC_{50} and E_{max} values of compounds are determined from dose-response curves. Right shifts of the dose response curve by the delta antagonist naltrindole are performed to verify that agonist activity is mediated through delta receptors.

Data analysis

The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test compounds was expressed as percentage of control SB. Values of IC_{50} and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prussoff equation. Mean ± S.E.M. values of IC_{50}, K_i and n_H were reported for ligands tested in at least three displacement curves. Biological data are tabulated on the following pages in Table 1.

Table 1: Biological data.

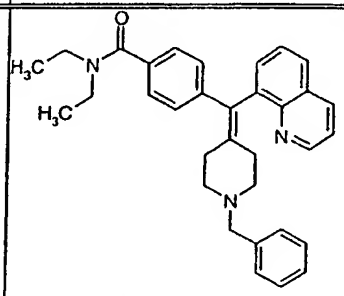
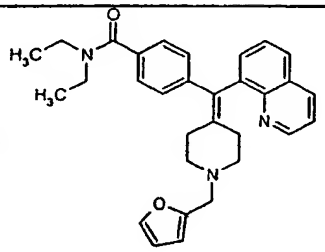
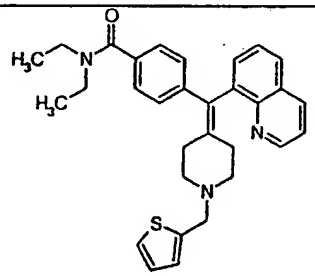
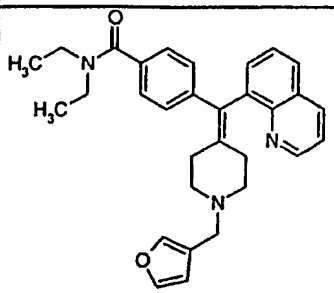
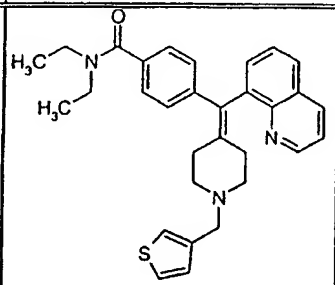
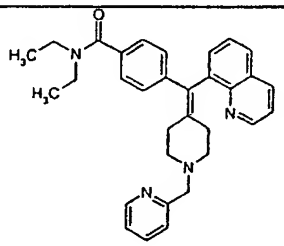
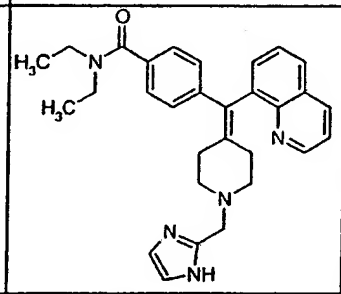
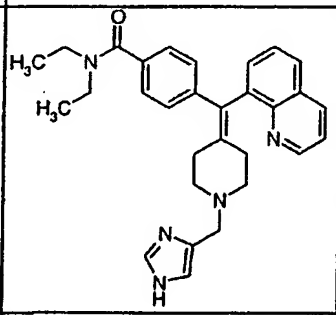
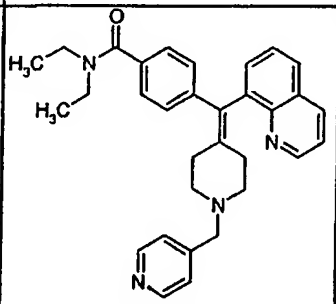
Ex. #	MOLECULAR STRUCTURE	HDELTA	HDELTA		RAT BRAIN		MOUSE BRAIN	
			EC50	% EMax	EC50	% EMax	EC50	% EMax
2		1.08	0.49	90.48	3.88	103.53	3.6	111.62
3		0.727	0.18	102.7	4.29	129.65	8.39	145.68
4		0.762	0.26	98.49	1.85	120.16	3.71	140.12
5		0.404	0.14	99.04	1.05	135.2	2.06	146.91

Table 1 (continued): Biological data.

Ex. #	MOLECULAR STRUCTURE	HDELTA	HDELTA		RAT BRAIN		MOUSE BRAIN	
			EC50	% EMax	EC50	% EMax	EC50	% EMax
6		0.549	0.38	122.78	3.45	134.62	4.41	140.21
7		0.563	0.25	97.6	2.32	126.28	2.88	124.31
8		0.381	0.28	110.98	3.84	148.15	4.59	138.38
9		0.808	1.9	100.25	38.34	112.17	59.61	122.69
10		0.765	0.8	118.41	33.5	108.52	37.8	110.11

Receptor saturation experiments

Radioligand Kδ values were determined by performing the binding assays on cell membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated Kδ (up to 10 times if amounts of radioligand required are feasible). The specific radioligand binding was expressed as pmole/mg membrane protein. Values of Kδ and B_{max} from individual experiments were obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

DETERMINATION OF MECHANO-ALLODYNIA USING VON FREY TESTING

Testing was performed between 08:00 and 16:00h using the method described by Chaplan et al. (1994). Rats were placed in Plexiglas cages on top of a wire mesh bottom which allowed access to the paw, and were left to habituate for 10-15 min. The area tested was the mid-plantar left hind paw, avoiding the less sensitive foot pads. The paw was touched with a series of 8 Von Frey hairs with logarithmically incremental stiffness (0.41, 0.69, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair was applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, and held for approximately 6-8 seconds. A positive response was noted if the paw was sharply withdrawn. Flinching immediately upon removal of the hair was also considered a positive response. Ambulation was considered an ambiguous response, and in such cases the stimulus was repeated.

TESTING PROTOCOL

The animals were tested on postoperative day 1 for the FCA-treated group. The 50% withdrawal threshold was determined using the up-down method of Dixon (1980). Testing was started with the 2.04 g hair, in the middle of the series. Stimuli were always presented in a consecutive way, whether ascending or descending. In the absence of a paw

withdrawal response to the initially selected hair, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. Optimal threshold calculation by this method requires 6 responses in the immediate vicinity of the 50% threshold, and counting of these 6 responses began when the first change in response occurred, e.g. the threshold was first crossed. In cases where thresholds fell outside the range of stimuli, values of 15.14 (normal sensitivity) or 0.41 (maximally allodynic) were respectively assigned. The resulting pattern of positive and negative responses was tabulated using the convention, X = no withdrawal; O = withdrawal, and the 50% withdrawal threshold was interpolated using the formula:

$$50\%\text{ g threshold} = 10^{(Xf + k_{\delta})} / 10{,}000$$

where Xf = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here $\delta = 0.224$.

Von Frey thresholds were converted to percent of maximum possible effect (% MPE), according to Chaplan et al. 1994. The following equation was used to compute % MPE:

$$\%\text{ MPE} = \frac{\text{Drug treated threshold (g) - allodynia threshold (g)}}{\text{Control threshold (g) - allodynia threshold (g)}} \times 100$$

ADMINISTRATION OF TEST SUBSTANCE

Rats were injected (subcutaneously, intraperitoneally, intravenously or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varied depending upon the nature of the test compound.

WRITHING TEST

Acetic acid will bring abdominal contractions when administered intraperitoneally in mice. These will then extend their body in a typical pattern. When analgesic drugs are administered, this described movement is less frequently observed and the drug selected as a potential good candidate.

A complete and typical Writhing reflex is considered only when the following elements are present: the animal is not in movement; the lower back is slightly depressed; the plantar aspect of *both* paws is observable. In this assay, compounds of the present invention demonstrate significant inhibition of writhing responses after oral dosing of 1-100μmol/kg.

(i) Solutions preparation

Acetic acid (AcOH): 120 μL of Acetic Acid is added to 19.88 ml of distilled water in order to obtain a final volume of 20 ml with a final concentration of 0.6% AcOH. The solution is then mixed (vortex) and ready for injection.

Compound (drug): Each compound is prepared and dissolved in the most suitable vehicle according to standard procedures.

(ii) Solutions administration

The compound (drug) is administered orally, intraperitoneally (i.p.) , subcutaneously (s.c.) or intravenously (i.v.)) at 10 ml/kg (considering the average mice body weight) 20, 30 or 40 minutes (according to the class of compound and its characteristics) prior to testing. When the compound is delivered centrally: Intraventricularly (i.c.v.) or intrathecally (i.t.) a volume of 5 μL is administered.

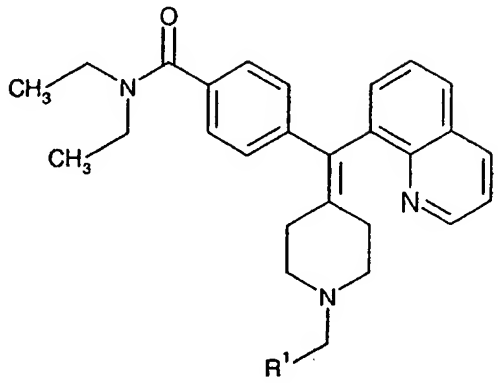
The AcOH is administered intraperitoneally (i.p.) in two sites at 10 ml/kg (considering the average mice body weight) immediately prior to testing.

(iii) Testing

The animal (mouse) is observed for a period of 20 minutes and the number of occasions (Writhing reflex) noted and compiled at the end of the experiment. Mice are kept in individual "shoe box" cages with contact bedding. A total of 4 mice are usually observed at the same time: one control and three doses of drug.

Claims

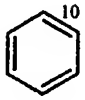
1. A compound of the formula I



I

wherein

R^1 is selected from any one of

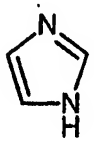


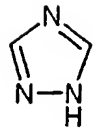
(i) phenyl ;

(ii) pyridinyl  ;

(iii) thienyl  ;

(iv) furanyl  ;

(v) imidazolyl  ;

(vi) triazolyl  ;

where each R^1 phenyl ring and R^1 heteroaromatic ring may independently be further substituted by 1, 2 or 3 substituents selected from straight and branched C_1-C_6 alkyl, NO_2, CF_3, C_1-C_6 alkoxy, chloro, fluoro, bromo, and iodo;

as well as salts thereof.

2. A compound according to claim 1, wherein each R^1 phenyl ring and R^1 heteroaromatic ring may optionally and independently be further substituted by 1, 2 or 3 substituents selected from methyl, CF_3, chloro, fluoro, bromo, and iodo.

3. A compound according to claim 1, wherein each R^1 phenyl ring and R^1 heteroaromatic ring may independently be further substituted by a methyl group.

4. A compound according to claim 1, wherein R^1 is pyridinyl, thienyl or furanyl.

5. A compound according to claim 1, selected from any one of

- N,N-Diethyl-4-(8-quinolinyl-N-benzyl-piperidin-4-ylidene-methyl)-benzamide;
- *N,N*-diethyl-4-[[1-(2-furylmethyl)-4-piperidinylidene](8-quinoline)methyl]benzamide;
- *N,N*-diethyl-4-{8-quinolinyl[1-(2-thienylmethyl)-4-piperidinylidene]-methyl}benzamide;
- *N,N*-diethyl-4-[[1-(3-furylmethyl)-4-piperidinylidene](8-quinolinyl)methyl]benzamide;

- *N,N*-diethyl-4-{8-quinolinyl[1-(3-thienylmethyl)-4-piperidinylidene]methyl}-benzamide;

- *N,N*-diethyl-4-[[1-(2-pyridinylmethyl)-4-piperidinylidene](8-quinolinyl)-methyl]benzamide;

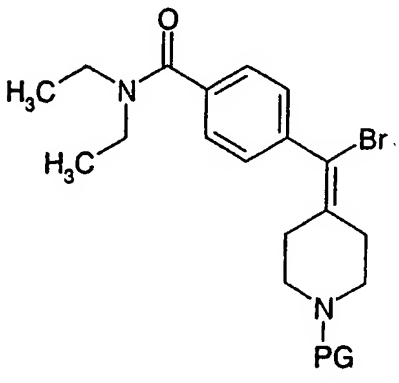
- *N,N*-diethyl-4-[[1-(1*H*-imidazol-2-ylmethyl)-4-piperidinylidene](8-quinolinyl)-methyl]benzamide;

- *N,N*-diethyl-4-[[1-(1*H*-imidazol-4-ylmethyl)-4-piperidinylidene](8-quinolinyl)-methyl]benzamide; and

- *N,N*-diethyl-4-[[1-(4-pyridinylmethyl)-4-piperidinylidene](8-quinolinyl)-methyl]benzamide.

6. A compound according to any of the preceding claims, in form of its hydrochloride, dihydrochloride, sulfate, tartrate, ditrifluoroacetate or citrate salts.

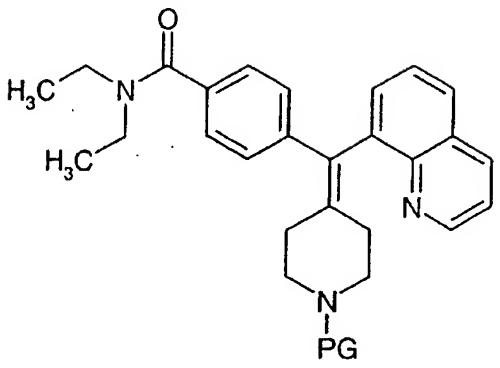
7. A process for preparing a compound of formula I, comprising the reaction of,
A) reacting a compound of the general formula II



- II

wherein PG is a urethane or benzyl-like protecting group with 8-quinolinyl boronic acid, using a palladium catalyst in the presence of a base to give the compounds of

general formula III,



III

which is thereafter deprotected, under standard conditions and alkylated under reductive conditions with a compound of the general formula R^1-CHO to give compounds of the general formula I

8. A compound according to claim 1 for use in therapy.

9. A compound according to claim 8, wherein the therapy is pain management.

10. A compound according to claim 8, wherein the therapy is directed towards gastrointestinal disorders.

11. A compound according to claim 8, wherein the therapy is directed towards spinal injuries.

12. A compound according to claim 5, wherein the therapy is directed to disorders of the sympathetic nervous system.

13. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of pain, gastrointestinal disorders, or spinal injuries.

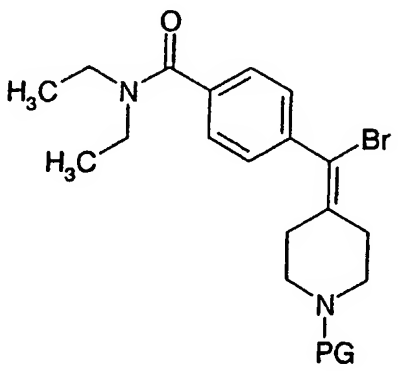
14. A pharmaceutical composition comprising a compound of the formula I according to claim 1 as an active ingredient, together with a pharmaceutically acceptable carrier.

15. A method for the treatment of pain, whereby an effective amount of a compound of the formula I according to claim 1 is administered to a subject in need of pain management.

16. A method for the treatment of gastrointestinal disorders, whereby an effective amount of a compound of the formula I according to claim 1, is administered to a subject suffering from said gastrointestinal disorder.

17. A method for the treatment of spinal injuries, whereby an effective amount of a compound of the formula I according to claim 1, is administered to a subject suffering from said spinal injury.

18. A compound of the general formula II



II

wherein PG is a urethane or benzyl-like protecting group.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00708

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/14, C07D 405/14, C07D 409/14, C07D 211/68, A61K 31/4523, A61P 25/04, A61P 25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9828275 A1 (ASTRA PHARMA INC.), 2 July 1998 (02.07.98), the claims, examples and compound 52 (page 55 and 58)	1-18
X	WO 9723466 A1 (ASTRA PHARMA INC.), 3 July 1997 (03.07.97), the claims, examples	1-6,8-17
X	WO 9933806 A1 (ORTHO-MCNEIL PHARMACEUTICAL, INC.), 8 July 1999 (08.07.99), the claims, examples	1-6,8-17

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2001	31-07-2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/BS Telephone No. +46 8 782 25 00

Form PCT ISA 210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00708

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Volume 42, 1999, Xiaoyan Zhang et al, "Probes for Narcotic Receptor Mediated Phenomena. 26.1-3 Synthesis and Biological Evaluation of Diarylmethylpiperazines and Diarylmethylpiperidines as Novel, Nonpeptidic & Opioid Receptor Ligands" page 5455 - page 5463 --	1-6,8-17
X	J. Med. Chem., Volume 43, 2000, Zhong-Yong Wei et al, "N,N-Diethyl -4- (phenylpiperidin -4 -ylidenemethyl) benzamide: A Novel, Exceptionally Selective, Potent & Opioid Receptor Agonist with Oral Bioavailability and Its Analogues", page 3895 - page 3905, page 3897, compound 8 and scheme 3 -- --------	7,18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/00708

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15-17
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/00708

Claims 15-17 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 01/00708

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9828275 A1	02/07/98	AU 5351298 A	17/07/98
		BR 9714055 A	09/05/00
		CN 1246111 A	01/03/00
		CZ 9902199 A	17/11/99
		EP 0946511 A	06/10/99
		IL 130535 D	00/00/00
		NO 993022 A	20/08/99
		PL 334374 A	28/02/00
		SE 9604785 D	00/00/00
		SK 76299 A	08/11/99
		TR 9901417 T	00/00/00
		US 6187792 B	13/02/01
		HU 0000610 A	28/09/00
		SE 9702535 D	00/00/00
WO 9723466 A1	03/07/97	AU 715547 B	03/02/00
		AU 1216297 A	17/07/97
		BR 9612204 A	13/07/99
		CN 1209124 A	24/02/99
		CZ 9801768 A	16/09/98
		EP 0915855 A	19/05/99
		HU 9901304 A	30/08/99
		IL 124996 D	00/00/00
		JP 2000502679 T	07/03/00
		NO 982807 A	19/08/98
		PL 327403 A	07/12/98
		SE 9504661 D	00/00/00
		SK 82298 A	04/11/98
		TR 9801180 T	00/00/00
		US 6130222 A	10/10/00
WO 9933806 A1	08/07/99	AU 2009799 A	19/07/99
		EP 1049676 A	08/11/00